

### 3 BACKGROUND OF THE INVENTION

5           The present invention is in the field of markers to be employed at  
6 biopsy sites to permanently mark the site, and to methods and apparatus for  
7 applying the permanent marker. More particularly, the present invention  
8 relates to a marker that is optimally adapted for marking biopsy sites in human  
9 breast tissue with permanently placed markers that are detectable by X-ray.

11 In modern medical practice small tissue samples, known as biopsy  
12 specimens, are often removed from tumors, lesions, organs, muscles and other  
13 tissues of the body. The removal of tissue samples may be accomplished by  
14 open surgical technique, or through the use of a specialized biopsy  
15 instruments such as a biopsy needle. A well known state-of-the-art instrument  
16 that is often used in connection with the practice of the present invention is  
17 known as the “vacuum assisted large core biopsy device”.

## SenoRx

are frequently used to devise a plan for the appropriate surgical procedure or other course of treatment.

Examination of tissue samples taken by biopsy, often by the above-mentioned "vacuum assisted large core biopsy sampler" is of particular significance in the diagnosis and treatment of breast cancer which is the most common cancer suffered by women in the U.S.A and elsewhere in the industrially developed world. Proper diagnostic procedures, frequent examination by well known techniques such as "mammography" and prompt subsequent surgical treatment have, however, significantly reduced the mortality rate caused by this form of cancer. For this reason, in the ensuing discussion of the pertinent background art and in the ensuing description the invention will be described as used for marking biopsy sites in human and other mammalian breast, although the invention is suitable for marking biopsy sites in other parts of the human and other mammalian body as well.

Thus, as is known, when an abnormal mass in the breast is found by physical examination or mammography a biopsy procedure follows almost invariably. The nature of the biopsy procedure depends on several factors. Generally speaking, if a solid mass or lesion in the breast is large enough to be palpable (i.e., felt by probing with the fingertips) then a tissue specimen can be removed from the mass by a variety of techniques, including but not limited to open surgical biopsy or a technique known as Fine Needle Aspiration Biopsy (FNAB). In open surgical biopsy, an incision is made and a quantity of tissue is removed from the mass for subsequent histopathological examination. In the FNAB procedure, a small sample of cells is aspirated from the mass through a needle and the aspirated cells are then subjected to cytological examination.

If a solid mass of the breast is small and non-palpable (e.g., the type typically discovered through mammography), a relatively new biopsy procedure known as "stereotactic needle biopsy" may be used. In performing

1 a stereotactic needle biopsy of a breast, the patient lies on a special biopsy  
2 table with her breast compressed between the plates of a mammography  
3 apparatus and two separate digital x-rays are taken from two slightly different  
4 points of view. A computer calculates the exact position of the lesion with X  
5 and Y coordinates as well as depth of the lesion within the breast. Thereafter,  
6 a mechanical stereotactic apparatus is programmed with the coordinates and  
7 depth information calculated by the computer, and such apparatus is used to  
8 precisely advance the biopsy needle into the small lesion. Usually at least five  
9 separate biopsy specimens are obtained from locations around the small lesion  
10 as well as one from the center of the lesion.

11 After the biopsy sample is taken, it may take several days or even a  
12 week before the results of the examination of the sample are obtained, and  
13 still longer before an appropriate treatment decision is reached. If the decision  
14 involves surgery it is clearly important for the surgeon to find the location in  
15 the breast from where the tumor tissue has been taken in the biopsy procedure,  
16 so that the entire tumor and possibly surrounding healthy tissue can be  
17 removed. For example, the particular treatment plan for a given patient may  
18 require the surgeon to remove the tumor tissue and 1 centimeter of the tissue  
19 surrounding the tumor. A co-pending application for United States Letters  
20 Patent by the same inventors discloses markers which are particularly well  
21 adapted for marking biopsy sites in the human breast, and which markers  
22 remain detectable by X-ray, ultrasound or some other detection technique only  
23 for a given time period (*i. e.* for 6 months) and slowly disappear thereafter, for  
24 example by absorption into the body. The purpose of such markers is to  
25 facilitate the surgical procedure that is performed while the marker is still  
26 detectable. The disappearance of the marker after a longer period of time may  
27 be advantageous to avoid obscuring or interfering with follow-up studies or  
28 further mammography or other imaging studies.

29 In connection with the background art the following specific printed art

1 is mentioned. United States Patent Nos. 2, 192, 270 and 5, 147, 307 describe  
2 visually discernible markers that are applied externally to the patient's skin.  
3 Radiographically (X-ray) detectable tissue markers (e.g., clips or staples) that  
4 are attached to tissue adjacent to the site from which the biopsy specimen has  
5 been removed, are described in International Patent Publication No. WO  
6 98/06346. Radiographically visible markers (e. g. marker wires) that may be  
7 introduced into the biopsy site and are inserted through the biopsy needle after  
8 a tissue sample is removed and which are thereafter allowed to remain  
9 protruding from the patient's body, are also described in WO 98/06346.  
10 However, due to the consistency of breast tissue and the fact that these biopsy  
11 site markers are typically introduced while the breast is still compressed  
12 between the mammography plates, these biopsy markers of the prior art may  
13 become attached to adjacent bands of connective tissue that do not remain at  
14 the specific location of the biopsy after the breast has been decompressed and  
15 removed from the mammography apparatus, and may suffer from additional  
16 disadvantages as well.

17 Thus, there is still a need in the art for of biopsy site markers that are  
18 deliverable into the cavity created by removal of the biopsy specimen and not  
19 into tissue that is located outside of that biopsy cavity, and which will not  
20 migrate from the biopsy cavity even when the breast tissue is moved,  
21 manipulated or decompressed. Moreover, such desired markers should  
22 remain detectable at the biopsy site *i. e.* within the biopsy cavity for an  
23 indefinite time period, and still should not interfere with imaging of the  
24 biopsy site and adjacent tissues at a later point of time, and most importantly  
25 should be readily distinguishable in the various imaging procedures from lines  
26 of calcifications which frequently are signs for a developing malignancy. The  
27 present invention provides such permanent biopsy site markers as well as  
28 apparatus and method for delivering such markers into the biopsy cavity.

29

## SUMMARY OF THE INVENTION

It is an object of the present invention to provide a biopsy site marker that is deliverable into the cavity created by removal of the biopsy specimen.

It is another object of the present invention to provide a biopsy site marker that does not migrate from the biopsy cavity even when the surrounding tissue is moved, manipulated or decompressed.

It is still another object of the present invention to provide a biopsy site marker that meets the foregoing requirements and that remains detectable at the biopsy site for an indefinite period of time.

It is yet another object of the present invention to provide a biopsy site marker that meets the foregoing requirements and that is readily distinguishable by X-ray from granules or lines of calcifications which frequently are signs for a developing malignancy.

It is a further object of the present invention to provide an apparatus and method for placing into the biopsy cavity a biopsy site marker that meets the foregoing requirements.

These and other objects and advantages are attained by a biopsy site marker that comprises small bodies or pellets of gelatin which enclose substantially in their interior a radio (X-ray) opaque object. The gelatin pellets are deposited into the biopsy site, typically a cylindrical opening in the tissue created by the recent use of a vacuum assisted large core biopsy device, by injection from an applicator through a tube that is placed into the biopsy site. Typically, several gelatin pellets, only some of which typically do, but all of which may contain the radio opaque object, are deposited sequentially from the applicator into the site through the tube. The radio opaque objects contained in the gelatin bodies have a non-biological shape or configuration to be identifiable as a man-made object such that in observation by typical mammography equipment, that is when viewed from at least two different viewing angles, they do not assume the shape of a line, whereby they are

1 readily distinguishable from granules or lines of calcification.

2       The features of the present invention can be best understood together  
3 with further objects and advantages by reference to the following description,  
4 taken in connection with the accompanying drawings, wherein like numerals  
5 indicate like parts.

## 6                   BRIEF DESCRIPTION OF THE DRAWINGS

7       **Figure 1** is a perspective view of a preferred embodiment of the biopsy  
8 site marker of the present invention.

9       **Figure 2** is a perspective view of a plurality of biopsy site markers in  
10 accordance with the first embodiment of the present invention.

11       **Figure 3** is a perspective view of an applicator apparatus in accordance  
12 with the present invention, for depositing the biopsy site marker at a biopsy  
13 site.

14       **Figure 4** is a perspective view of the applicator apparatus of Figure 3,  
15 showing the applicator with an extended piston indicating that the applicator  
16 is loaded with biopsy site markers.

17       **Figure 5** is a cross-sectional view of the site marker shown in Figure 4,  
18 the cross section taken on lines 5,5 of Figure 4.

19       **Figure 6** is an enlarged cross sectional view showing the applicator of  
20 Figure 4 loaded with biopsy site markers in accordance with the present  
21 invention.

22       **Figure 7** is a schematic view of a human breast, showing a biopsy  
23 cavity of the type obtained by a vacuum assisted large core biopsy sampler,  
24 into which a plurality of biopsy markers are deposited in accordance with the  
25 present invention.

## 26                   DESCRIPTION OF THE PREFERRED EMBODIMENTS

27       The following specification taken in conjunction with the drawings  
28 sets forth the preferred embodiments of the present invention. The  
29 embodiments of the invention disclosed herein are the best modes

1 contemplated by the inventors for carrying out their invention in a commercial  
2 environment, although it should be understood that various modifications can  
3 be accomplished within the parameters of the present invention.

4 Referring now to the drawing figures and particularly to **Figures 1** and  
5 **2**, a body **20** of gelatin or reconstituted collagen in the shape of a pellet that  
6 includes or incorporates a radio-opaque marker **22** of a definite shape is  
7 disclosed. The gelatin or reconstituted collagen body **20** can be of virtually  
8 any shape or configuration, however the herein shown shape of a cylinder or  
9 pellet is preferred. The gelatin body of pellet **20** is of such size that several of  
10 the pellets can be deposited in a biopsy site, such as a typical biopsy site  
11 obtained by using the vacuum assisted large core biopsy device that is  
12 frequently used in current medical practice. The gelatin body or pellet **20** is  
13 stored and is applied, that is deposited in the biopsy site, in a dehydrated form  
14 through an applicator device that forms another aspect of this invention.  
15 However, when the gelatin body or pellet **20** of the invention is not deposited  
16 through the applicator device, it does not necessarily need to be stored and  
17 applied in a dehydrated form. Nevertheless, storing the gelatin pellets **20** in  
18 dehydrated form increases their useful shelf-life and renders it easier to keep  
19 them sterile.

20 After having been deposited at the biopsy site the gelatin marker **20**  
21 slowly absorbs moisture from the surrounding tissue and becomes hydrated.  
22 In the dehydrated form, shown in the appended drawing figures, the gelatin  
23 body or pellet **20** is approximately 1 to 3 mm in diameter and is approximately  
24 5 to 10 mm long. The presently preferred embodiment of the gelatin pellet **20**  
25 is approximately 2 mm in diameter and is approximately 8 mm long. After  
26 the pellet **20** has reached hydration equilibrium with the surrounding tissue it  
27 becomes approximately 3 to 5 mm in diameter and approximately 10 to 15  
28 mm long. After hydration the presently preferred embodiment of the pellet **20**  
29 is approximately 4 mm in diameter and approximately 10 mm long.

1           The gelatin or reconstituted collagen material itself is observed under  
2 ultrasound examination as a white spot because of the air pockets usually  
3 entrapped in its matrix. In mammography the gelatin is observed as dark  
4 spots in normal breast, because of the presence of the air pockets. In a fatty  
5 breast viewed by mammography the gelatin marker is observed as a lighter  
6 area containing dark spots, due to the water in the hydrated gelatin absorbing  
7 more energy than the surrounding matrix and the air pockets within the  
8 matrix. A pellet 20 or plurality of pellets 20 due to their bulk may also be  
9 palpable and locatable by tactile means within the breast tissue or other tissue.  
10 The gelatin or reconstituted collagen marker itself can be made even more  
11 radio-opaque by ion-impregnation and chelation techniques which are  
12 described in detail in the aforesaid co-pending application serial number  
13 09/241,936 filed on February 2, 1999 by the same inventors in connection  
14 with the description of biopsy markers of that application, and the description  
15 of this method of rendering the gelatin markers radio-opaque is also provided  
16 here below. The disclosure of co-pending application serial number  
17 09/241,936 is incorporated herein by reference in its entirety. The gelatin or  
18 reconstituted collagen material can also be made more radio-translucent by  
19 entrapping (mixing) a substantial amount of air in the gelatin. Moreover, a  
20 visually detectable substance, such as carbon particles, or a suitable dye (*e. g.*  
21 methylene blue or indigo) may also be added to the gelatin to make the marker  
22 visible by a surgeon during dissection of the surrounding breast tissue.

23           The gelatin or reconstituted collagen *per se* does not serve as a  
24 permanent marker of the biopsy site because it is eventually reabsorbed by the  
25 body, although the dye or even ionic material that made the gelatin visible or  
26 radio-opaque, respectively, may remain at the site for longer time period than  
27 the palpable gelatin pellet, and may remain there indefinitely. Factors which  
28 influence how long the gelatin or reconstituted collagen pellet remains at the  
29 site, and various means to adjust this time period are described in the afore-



1 mentioned co-pending application serial number 09/241,936.

2       It is a novel and important aspect of the present invention to  
3 incorporate into the gelatin or reconstituted collagen body or pellet **20** the  
4 radio-opaque marker **22**. The radio-opaque or X-ray detectable marker **22**  
5 that is incorporated or enclosed in the gelatin pellet **20** must have the  
6 following properties. First, by its very nature it must be detectable by X-ray,  
7 including the type of radiography used in the practice of mammography. It  
8 must be comprised of a material or composition that is not absorbed by the  
9 body and stays for indefinite time at the biopsy site, retains its shape and  
10 remains X-ray detectable at the biopsy site also for an indefinite time. The  
11 material or composition of the radio-opaque marker **22** must, of course, be  
12 biocompatible at the site where it is deposited. Another important  
13 requirement is that the biocompatible marker must have an identifiable  
14 specific non-biological shape or form. The purpose of specific form for the  
15 marker is to render the marker distinguishable under X-ray or in a  
16 mamographic examination from naturally formed calcification granules or a  
17 line of such granules, which are also X-ray opaque. As is known, a line of  
18 calcification which normally forms along ducts is considered a sign of  
19 developing malignancy. Thus, the marker **22** should be of such specific  
20 configuration that when it is viewed sterically, as during a mammography  
21 examination, it should be distinguishable from an X-ray opaque line.  
22 Numerous specific shapes or configurations satisfy the foregoing  
23 requirements, however amorphous X-ray opaque material that would be  
24 uniformly (or substantially uniformly) distributed in the gelatin pellet **20** is  
25 unlikely to satisfy these requirements.

26       Materials or compositions which are suitable for the marker **22** include  
27 metal, such as stainless steel, tantalum, titanium, gold, platinum, palladium,  
28 various alloys that are normally used in bioprosthesis and ceramics and metal  
29 oxides that can be compressed into specific shapes or configurations. Among

1 these the use of biocompatible metals is presently preferred, and the herein  
2 described preferred embodiment of the marker 22 is made of stainless steel.  
3 Generally speaking the marker 22 is approximately 0.010 to 0.060 inches  
4 wide, approximately 0.030 to 0.200 " long and approximately 0.002 to 0.020 "  
5 thick. The presently preferred permanent marker 22 shown in the drawing  
6 figures has the configuration or shape approximating an upside down turned  
7 Greek letter gamma ( $\gamma$ ), is approximately 0.10" long and approximately 0.040  
8 " wide. The upside-down Greek letter gamma ( $\gamma$ ) shape is believed to be  
9 unique, has some resemblance to the popular breast cancer awareness ribbon  
10 and is readily distinguishable under X-ray and mammography as a "man-  
11 made" marker object from any naturally formed X-ray opaque body. Various  
12 manufacturing techniques which *per se* are well known in the art, can be  
13 utilized to manufacture the X-ray opaque permanent marker 22. Thus, the  
14 marker 22 can be formed from wire, or can be electrochemically etched or  
15 laser cut from metal plates. The presently preferred embodiment of the  
16 gamma ( $\gamma$ ) shaped marker 22 is formed by electrochemical etching from  
17 stainless steel plates.

18       **Figures 1, 2** and the other drawing figures, as applicable, show only  
19 one marker in the gelatin pellet 20, although more than marker may be  
20 incorporated in the pellet 20. **Figure 1** discloses a cylindrically shaped gelatin  
21 pellet 20 that in accordance with the present invention includes the gamma  
22 ( $\gamma$ ) shaped stainless marker 22, and as an optional feature also includes a dye  
23 or other coloring material (*e. g.* indigo) that also stays substantially  
24 permanently at the biopsy site and is visible by a surgeon when the breast  
25 tissue is dissected, as in an operation where tumor tissue is removed  
26 (lumpectomy).

27 Gelatin bodies or pellets 20 all of which include one or more permanent radio  
28 opaque markers 22 in accordance with the present invention may be deposited

1 at a biopsy site. Alternatively, a series of gelatin bodies or pellets 20 where  
2 only some but not all include a permanent X-ray opaque marker 22 of unique  
3 non-biological shape, may be deposited at the biopsy site. Preferably, a series  
4 of pellets 20 are deposited where each second, each third, or each fourth etc.,  
5 pellet includes the marker 22. Figure 2 discloses an example of a series or  
6 sequence of pellets 20 where each second pellet 20 includes the metal marker  
7 22 and where each pellet 20 that does not include the metal marker 22  
8 includes carbon black or dye that is visible to the surgeon during operation.  
9 In this connection it should be understood and appreciated that as noted above  
10 the gelatin bodies or pellets 20 themselves serve a purpose of marking the  
11 biopsy site for a predetermined length of time, that is until they become  
12 absorbed by the body.

13 The drawing figures, particularly Figures 1 and 2 show the metal  
14 marker 22 disposed substantially in the center of the cylindrical gelatin pellet  
15 20. This is preferred but is not necessary for the present invention. The  
16 metal marker 22 can be embodied in or included in the gelatin body 20  
17 virtually anywhere. The gelatin body or pellet 20 however has to have  
18 sufficient integrity or firmness to retain the metal marker 22 and air bubbles  
19 which are usually deliberately entrapped in the gelatin. As is known, the  
20 firmness or bodily integrity of gelatin is measured in units of Bloom.  
21 Generally speaking it was found in accordance with the present invention that  
22 the higher the Bloom strength of the gelatin used in the marker 20 the better  
23 the marker performs. The higher Bloom strength gelatin holds gas bubbles  
24 within its matrix better than lower Bloom strength gelatin. Gelatin with a  
25 Bloom strength of approximately 150 especially 175 is adequate for the  
26 practice of the present invention, but a more preferred range is 200 to 300  
27 Bloom, the most preferred range being between 250 and 300. (For  
28 comparison, typical food gelatin is approximately 75 Bloom, and gelatin of  
29 300 Bloom feels like a soft rubber eraser.)

1           A description how to obtain gelatin or reconstituted collagen bodies  
2   suitable for use as markers 20 with various properties, before the permanent  
3   radio-opaque metal or like marker 22 of specific form is incorporated therein,  
4   is provided below in connection with following examples.

5   **Example of Radiographically Visible/Palpable Marker Material Formed**  
6   **of Metal Ions In Combination With a Collagenous or Gelatinous Matrix**

7           United States Patent No. 4,847,049 (Yamamoto incorporated herein by  
8   reference) describes an ion-impregnation or chelation technique whereby an  
9   ion may be impregnated or chelated to collagen for the purpose of imparting  
10   antimicrobial properties to the collagen preparation. Thus, using this  
11   technique, imageable ions such as radiographically visible metal ions, may be  
12   bound to a bulky collagenous material to form a marker 10 that may be a)  
13   imaged by radiographic means and b) located by palpation of tissue  
14   surrounding the biopsy site. For example, a silver ion-renatured collagen  
15   composition may be prepared by the following process:

16   **Step 1-Renaturation of Collagen (or Gelatin):**

17           Collagen may be renatured to an insoluble form by processing of  
18   denatured collagen that has been obtained from a natural source such as  
19   bovine corium (hide), bovine tendon, and porcine skin. Alternatively, pre-  
20   processed, insoluble collagen may be purchased in the form of a commercially  
21   available hemostatic material such as Collastat™ and Avitene™ nonwoven  
22   web. Methods for renaturing collagen are known in the literature, including,  
23   for example, those methods described in United States Patent Nos. 4,294,241  
24   and 3,823,212. The specifications of United States Patent Nos. 4,294,241 and  
25   3,823,212 are incorporated herein by reference.

26           A particularly preferred form of renatured collagen for utilization in  
27   accordance with the present invention is one that has been renatured *and*  
28   covalently cross-linked. This collagen may be prepared by utilizing readily  
29   available polyfunctional cross linking agents or fixatives, such as dialdehydes,

1 dicarboxylic acids, diamines, and the like. Typically, tropocollagen is  
2 dissolved in a buffer of pH 3.0 to 5.0 to provide a solution containing  
3 approximately 1 to 2% by weight of the collagen. Then 1% of a dialdehyde  
4 cross-linking agent such as glutaraldehyde or formaldehyde is then added.  
5 The mixture is then frozen and stored for approximately 24 hours. After  
6 thawing and washing to remove unreacted cross linking agent, the renatured  
7 cross-linked collagen is then ready for contact with a silver ion-containing  
8 solution.

#### 9 Step 2-Binding of Metal Ions to the Renatured Collagen:

10 The source of silver ion may be a water soluble silver salt, preferably  
11 silver nitrate. While the concentration of the silver ion in the solution is not  
12 particularly critical, it will be usually convenient to utilize solutions in the  
13 concentration range of about 10 to 10 millimolar.

14 The renatured collagen is preferably contacted with a silver ion-  
15 containing solution in the pH range of about 4 to 9. The pH of the silver ion-  
16 containing solution can be controlled by the addition of an appropriate  
17 titrating agent, such as nitric acid, or potassium hydroxide, as required, to  
18 maintain the pH at less than about 9.0 to avoid the degradation of the silver.  
19 There is not believed to be any lower limit for the pH, however, normally a  
20 pH above 4.0 will be convenient. A particularly preferred range for the pH is  
21 from 7.0 to 7.5. The binding capacity of silver by collagen is particularly  
22 effective within this preferred pH range, although the amount of binding by  
23 silver by the collagen is further controllable by the concentration of the silver  
24 ion-containing solution and/or exposure time of the collagen to the silver ion-  
25 containing solution. Simultaneous with or subsequent to exposure of the  
26 collagen to the silver ion-containing solution, the collagen is then exposed to  
27 ultraviolet radiation of energy and duration sufficient to strengthen the  
28 binding of the silver ions to the collagen without substantial formation of  
29 metallic silver formed as a result of oxidation of various functional groups in

1 the collagen by the silver ion. While the exact limits of the ranges of the  
2 conditions which will be sufficient to strengthen the binding of the silver ions  
3 without substantial formation of metallic silver are not precisely determinable,  
4 it will generally suffice to maintain the pH of the silver-collagen environment  
5 at less than 8.0 while exposing the collagen to ultraviolet radiation in the  
6 range of about 210 to 310 nm wavelength for about from 5 to 15 minutes. The  
7 time of UV exposure for complete reaction is inversely proportional to the  
8 light intensity which is preferably in the range of 100 to 1,000  
9 microwatts/cm<sup>2</sup>. A slight coloration of the collagen due to the exposure to  
10 ultraviolet radiation is acceptable, i.e., a turning from white to a light brown to  
11 yellow color, indicating a slight oxidation reaction occurring in the collagen,  
12 however, the radiation should not be to the extent that dark brown or black  
13 areas in the collagen occur due to over-oxidation and/or substantial formation  
14 of metallic silver. Normally the exposure will be performed at ambient  
15 temperatures, i.e., in the range of about 20 degrees to 25 degrees C, however,  
16 there is not believed to be any reason why the exposure could not occur at  
17 higher or lower temperatures providing that the temperature is not high  
18 enough to cause degradation of the collagen and/or silver ion. There is not  
19 believed to be any lower limit to the temperature at which the exposure may  
20 take place, provided it is above the freezing point of the ion-containing  
21 solution.

22 Ultraviolet radiation may be provided by any conventional ultraviolet  
23 radiation source of appropriate wavelength, such as germicidal lamps and  
24 mercury/xenon lamps.

25 Step 3 (optional)-Addition of Visible Marker Component to the  
26 Collagen or Gelatin Matrix:

27 If it is desired for the marker to be detectable visually, as well as by  
28 imaging and palpation, a quantity of a visible substance having a color  
29 dissimilar blood or tissue may be added. For example, carbon particles or a

1 dye (e.g., methylene blue, indigo) may be added to the above-prepared silver  
2 ion/collagen preparation to provide a colored silver ion/collagen marker 10  
3 that is imageable (by radiographic means), palpable (by hand) and visible  
4 (under white light in the operating room).

5 The above-described collagen-metal ion marker 10 (with or without  
6 visible marker component) is introduced into the cavity created by removal of  
7 the biopsy specimen. The quantity of this marker 10 introduced may be  
8 sufficient to distend or stretch the biopsy cavity somewhat, thereby creating a  
9 more palpable and obvious mass of marker material at the biopsy site.

10 Renatured gelatin or a cross-linked gelatin preparation such as  
11 Gelfoam™ may be impregnated or combined with a metal ion to provide a  
12 gelatin-metal ion marker material. The gelatin may be prepared and ion-  
13 bound by the same method as set forth hereabove for collagen.

14 Example of Radiographically or Ultrasonically Visible/Palpable Marker  
15 Material Formed of a Gas in Combination With a Collagenous or  
16 Gelatinous Matrix

17 Step 1-Renaturation of Collagen (or Gelatin):

18 Collagen or gelatin is renatured, as by the method described in Step 1  
19 of the immediately preceding example and described in the literature,  
20 including, for example, those methods described in United States Patent Nos.  
21 4,294,241 and 3,823,212.

22 Step 2-Dispersing of Air or Other Gas in the Renatured Collagen or Gelatin  
23 Matrix

24 Air or another biologically inert gas (e.g., carbon dioxide) is then  
25 dispersed throughout the renatured collagen or gelatin matrix by a suitable  
26 means such as mixing, mechanical blending, nucleation, bubbling, etc. This  
27 results in the formation of many small gas bubbles throughout the collagenous  
28 or gelatinous matrix and provides a marker substance that can be introduced  
29 into the biopsy cavity through a cannula or tube and is substantially more

1 radio-lucent than the tissue surrounding the biopsy cavity. In this regard, this  
2 marker can be imaged by x-ray or ultrasound but will not block or obscure  
3 imaging of tissue that lies immediately adjacent the biopsy cavity. Also,  
4 because of the bulk of the collagen or gelatin matrix, the marker is readily  
5 palpable and locatable by tactile means within the surrounding breast tissue or  
6 other tissue.

#### 7 Step 3 (optional)-Addition of Visible Marker Component:

8 If it is desired for the marker to be detectable visually, as well as by  
9 imaging and palpation, a quantity of a visible substance having a color  
10 dissimilar to blood or tissue may be added. For example, carbon particles or a  
11 dye (e.g., methylene blue, indigo) may be added to the above-prepared silver  
12 ion/collagen preparation to provide a colored silver ion/collagen marker 10  
13 that is imageable (by radiographic means), palpable (by hand) and visible  
14 (under white light in the operating room).

15 In routine use, the above-described collagen/gas or gelatin/gas marker  
16 10 (with or without visible marker component) is introduced into the cavity  
17 created by removal of the biopsy specimen. The quantity of this marker 10  
18 introduced may be sufficient to distend or stretch the biopsy cavity somewhat,  
19 thereby creating a more palpable and obvious mass of marker material at the  
20 biopsy site.

#### 21 Preferred Example of Preparing Cylindrically Shaped Gelatin Pellets 20 22 Having a Colorant and Including the Permanent Marker 22

23 80 grams of dry gelatin obtained from porcine skin is mixed into 1000  
24 ml of hot water (180 °F). Variations in gelatin to water ratio will change the  
25 consistency but are nevertheless permissible within the scope of the invention.  
26 The 80 grams of gelatin is about the maximum amount which will dissolve in  
27 water without modifications to pH. The gelatin is then fully dissolved in the  
28 water with slight mixing. In a separate container, 1.6 grams of indigo  
29 colorant is mixed into 20 ml of ethyl alcohol. Then the ethanol solution of the



1 colorant is added by mixing to gelatin dissolved in water. Air is then  
2 whipped into gelatin mixture to froth the mixture .

3 The gelatin dissolved in water is then poured into molds (not shown)  
4 which have the shape of the desired gelatin body. In the preferred  
5 embodiment the mold is shaped to provide the cylindrical pellet shown in the  
6 drawing figures. One gamma ( $\gamma$ ) shaped permanent marker 22, made by  
7 chemical etching from stainless steel plates, is deposited into the gelatin in  
8 each mold. (In alternative embodiments more than one marker 22 may be  
9 deposited into each mold.) Due to the viscosity of the gelatin solution the  
10 marker 22 does not usually sink to the bottom of the mold. The top of the  
11 plate (not shown) holding a plurality of molds is squeegeed to level the  
12 mixture.

13 After cooling to approximately 40 ° F or cooler temperature the gelatin  
14 sets and provides the gelatin body 20 that incorporates the permanent marker  
15 22. However, in order to dehydrate the marker it is first frozen and thereafter  
16 lyophilized in commercial lyophilization apparatus. Gelatin pellets containing  
17 the permanent marker 22 but not having a colorant can be prepared in the  
18 same manner, but without adding indigo dye or other colorant. Gelatin bodies  
19 or markers 20 that do not include or incorporate a permanent marker 22 can  
20 also be made in this manner, but without depositing the marker 22 into the  
21 gelatin after it has been placed into the mold. The gelatin body 20 prepared in  
22 this manner is reabsorbed from the biopsy site by the human body in  
23 approximately three weeks, whereas the permanent marker 22 remains  
24 indefinitely.

25 Description of the Applicator Apparatus and its Use in Conjunction with  
26 the Biopsy Marker of the Invention

27 Referring now to **Figures 3 - 7** the applicator device or apparatus 24  
28 with which the biopsy markers of the invention are preferably applied or  
29 deposited, is disclosed. In this connection it should be understood that the

1 biopsy markers of the invention can be used without the applicator, and can be  
2 deposited in accordance with the various methods and techniques utilized in  
3 the state-of-the-art. However, a preferred technique of applying the biopsy  
4 markers of the invention is to place or deposit them in a biopsy cavity that is  
5 obtained with a vacuum assisted large core biopsy device of the type presently  
6 used in the state-of-the-art. Such a device, distributed for example by Johnson  
7 and Johnson Endo Surgery is well known in the art, and is schematically  
8 shown in **Figure 7**.

9       The applicator **24** of the invention comprises an elongated cylindrical  
10 body **26** having an interior cavity and a piston **28** that fits and slides back and  
11 forth in the elongated cylindrical body **26**. The cylindrical body **26** has an  
12 enlarged disk **30** at one end **32**. The disk **30** serves to render it convenient for  
13 a user (not shown) to operate the applicator **24**, as is described below. The  
14 cylindrical body **26** that can also be described as an elongated flexible tube  
15 has an opening **34** that commences a relatively short distance, that is  
16 approximately 0.3 “ before its other, closed end **36**. The opening **34** is  
17 configured to form a ramp in the side of the tube **26**. The outer diameter of  
18 the tube **26** is such that it fits through the vacuum assisted large core biopsy  
19 device **38** shown in **Figure 7**. In this connection it should of course be  
20 understood that the precise dimensions of the tube **26** are coordinated with the  
21 dimensions of the piston **28** and with the vacuum assisted large core biopsy  
22 device **38**. Moreover, the diameter of the gelatin pellets **20** in their  
23 dehydrated form are also coordinated with the inner diameter of the cylinder  
24 or tube **26**. The cylinder or tube **26** and the piston **28** can be made from any  
25 appropriate medical grade plastic material, and is preferably made of high  
26 density polyethylene. The outer diameter of the presently preferred  
27 embodiment of the cylinder or tube **26** is approximately 0.093 “ and its inner  
28 diameter is approximately 0.070 “.

29       In the preferred manner of using the biopsy markers of the present

1 invention having the permanent markers 22 incorporated in a gelatin body 20,  
2 as well as using biopsy markers that have only the gelatin body 20 without a  
3 permanent marker 22, the applicator device 24, more precisely the tube 26 is  
4 loaded with a desired number of pellets 20, as is shown in **Figures 4 - 6**. Any  
5 number of pellets 20 within the range of 1 to approximately 30 may be loaded  
6 within the tube 26, however presently it appears that approximately 8 pellets  
7 20 are optimal for being loaded into the tube 26 and to be deposited in a  
8 biopsy cavity where approximately 1 gram of tissue had been removed. Such  
9 a biopsy cavity 40 in a human breast 42 is schematically illustrated in **Figure**  
10 **7**. The pellets 20 which are loaded into the applicator tube 26 may all include  
11 the permanent marker 22, but it is presently preferred that only every other  
12 pellet 20 loaded into the applicator tube 26 have the permanent marker 22.  
13 Such an array of 8 pellets 20, alternating between pellets with and without  
14 permanent markers 22 is shown in **Figure 2**.

15 When the pellets 20 are in the tube 26 the piston 28 is extended, as is  
16 shown in **Figures 4 and 5**. The pellets 20 are expelled one-by-one from the  
17 tube 26 through the ramp-shaped opening 34 as the piston 28 is pushed into  
18 the cylinder or tube 26. During this process the closed end 36 of the tube 26  
19 is disposed in the cavity 40 formed by biopsy sampling. It is contemplated  
20 that the dispersed radio-opaque permanent markers 22 provide a good  
21 definition of the entire biopsy cavity 40 for subsequent observation or surgical  
22 procedure. **Figure 3** illustrates the applicator device 24 after the pellets 20  
23 have been expelled from the applicator tube 26.